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RESULTS OF BLOOD CULTURES IN RHEUMATOID ARTHRITIS *

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During the past 2 years we have made bacterial cultures from the blood of a large number of patients representing a wide variety of clinical conditions. We wish to present here a summary of the results in those cases in which acute or chronic involvement of the joints and adjacent tissues were the predominant or prominent clinical features. The literature contains few reports of this character. Rosenow¹ reports the isolation of a nonhemolytic streptococcus from the blood in 5 of 9 cases of rheumatic fever during the height of the attack, and occasionally in cases of proliferating osteoarthritis, arthritis deformans. By making cultures directly from the glands draining the involved joints in 54 cases, he isolated a modified Strep. viridans from 32 cases, staphylococcus in 5 cases, B. mucosus in 3 cases, B. welchii in 14 cases, and a diphtheroid bacillus in 5 cases. M. catarrhalis and the gonococcus were isolated once each. He found organisms in the joint fluid in a number of cases.

The method we used for blood cultures was essentially that of Rosenow. Fifteen c.c. or more of blood were drawn directly into a flask containing a sterile 0.5% solution of sodium citrate in distilled water. In 1½-2 hours, hemolysis being complete, the entire flask was centrifuged at 3000 revolutions per minute for 20-30 minutes. The supernatant fluid was drawn off and the sediment, consisting of leukocytes, stroma of red corpuscles and whatever bacteria were present, was rewashed with sterile water and centrifuged to free it further from hemoglobin. This sediment was then planted in various culture media under varying conditions of oxygen tension. Occasionally organisms developed in the glucose-ascitic broth, but more frequently minute colonies of streptococci were found in the deeper portions of tall shake-cultures in glucose-ascitic agar, where partial anaerobic conditions were present. Frequently the colonies would be visible as minute whitish specks in 2 or 3 days, but very often they developed

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¹ Jour. Am. Med. Assn., 1914, 63, p. 905.

more slowly. We often found streptococci by staining a smear from the sediment in the depths of agar-shake tubes which in 10 days of incubation had developed no visible colonies.

We make no attempt in this report to differentiate the types of conditions by using the terms osteoarthritis, proliferating arthritis, para-arthritis, etc. For convenience we have grouped the cases as acute and chronic, although these evidently are arbitrary terms, and the line cannot be sharply drawn which separates the groups. Cases of relatively short duration, with acute pain, fever, leukocytosis, etc., were considered acute. Those of longer standing with less pain and with little or no elevation of temperature we classed as chronic. Obviously as the one shades into the other a satisfactory differentiation is difficult.

Following are detailed histories of a few representative cases of different types:

1.—Merchant, aged 31. Attacks of inflammatory rheumatism 7 and 4 years previous, with apparently good recovery. For past 10 weeks an irregular intermittent temperature up to 104 F.; general weakness and pain in all the large joints, especially the hips.

The liver and spleen were much enlarged. There was tenderness in the region of the gallbladder. The heart was enlarged to the left and had a diffuse impact at the apex. There was a low pitched systolic murmur at the apex. Pulse was irregular in rate, 60-120. Blood pressure 125. Hemoglobin 60 per cent., whites 6600, polymorphonuclears 88 per cent.

Enlarged joints were extremely painful on pressure or motion; they showed no local redness but had an increased local temperature.

Diagnosis showed acute arthritis and acute mitral endocarditis.

The blood culture gave a gram-positive diplococcus which did not cause hemolysis nor produce a noticeable greenish tint on blood agar plates. Chain formation was not noticeable at first but after several generations of subcultures it became marked. This organism was classified as a nonhemolytic streptococcus.

A half-grown rabbit injected intravenously with the growth from the surface of a blood agar slant died within 48 hours. The mitral valve contained hemorrhagic points. Both hip joints were congested and contained increased fluid. The injected organism was recovered from the heart's blood and from the joint fluid.

2.—Man, aged 45. Complained of pain and stiffness in lumbar region, in right leg and neck. These points were very sensitive to pressure. Duration was 2 years.

The blood picture was normal. The Wassermann test was negative.

Roentgen rays showed a fusion of the vertebrae and proliferation of bone in the cervical and lumbar regions.

Diagnosis showed chronic myositis and proliferating arthritis.

The blood culture gave a nonhemolytic, nongreen-producing streptococcus. Second culture 3 weeks later gave the same result.

Growth from 2 blood agar slants injected intravenously into a young rabbit. Four days later the rabbit had impairment of motion in the hind quarters; lost weight steadily, would not eat, and moved about only after persistent provocation. Was chloroformed on the 12th day after inoculation. The mus-

culature was pale and flabby throughout, the viscera were somewhat injected and a phlegmonous infiltrating abscess was present in the gluteal muscles. The lumbar vertebrae were studded with hemorrhagic points and around and between the vertebrae was a seropurulent fluid which contained numerous streptococci.

3.—Woman; pain and deformity of joints of the extremities with markedly impaired mobility. Examination showed extensive pyorrhea alveolaris with badly decayed teeth.

The blood culture gave *B. capsulatus*, a vaccine of which was given; dental repairs were made to remove, if possible, the source of infection. Following this the patient was entirely free from pain, and the swelling and deformity of the joints was slowly improved, with increased mobility.

A year later there were symptoms of recurrence of tenderness and swelling in the joints. A 2nd blood culture resulted in isolating organism similar to the 1st. Vaccine treatment again was followed by relief. Whether this was permanent is not known as the patient was lost from observation.

4.—Man, aged 30; 6 years ago, following an attack of grip, the patient had acute rheumatic fever which kept him in bed 10 weeks. A stiffness of the joints of the back and hips developed.

The entire lower portion of the vertebral column was fixed and immobile, a typical 'poker-spine.' The hip joints also were immobile. Patient was able to walk after a fashion, with the body bent forward at an angle of about 90 degrees, crossing the legs in front of each other at each step by flexion of the knees. He had slight pain in the affected region. General condition of health good. The tonsils were enlarged and contained masses of cheesy material.

The blood culture gave a nonhemolytic streptococcus.

The tonsils were removed. An autogenous vaccine was given, and the reaction following the 1st few injections of this consisted of an intense aching pain in the affected joints. On subsequent injections there was no reaction and the patient had complete freedom of pain. His active symptoms subsided, but as would be expected, the ankylosis was permanent.

5.—Woman, aged 64. Two years ago gradual stiffening with soreness and pain began in the joints of the hands. Later the elbows, shoulders and knees were involved progressively and at time of examination scarcely a joint in the entire body was free from the affection. The sterno-mastoid muscles became sore and contracted spasmodically, at short intervals continuously, causing extreme discomfort.

The blood culture gave a nonhemolytic streptococcus.

The tonsils were removed; they contained numerous streptococci throughout their structure.

Persistent vaccine treatment was carried out using the organism obtained from the blood. The patient was given strict rest and attention was given to diet and hygienic conditions. Marked improvement followed. The general soreness and pain in the joints disappeared.

6.—Man, aged 35. Had a streptococcal skin infection of 1 finger from which a hemolytic streptococcus was isolated. The entire hand became red, swollen and painful, with red streaks running up the arm. The epitrochlear and axillary nodes became swollen and painful. Local infection subsided following free drainage and continuous hot moist dressings. Almost immediately the knee joints became enlarged and tender to movement and pressure. This was followed by severe involvement of the vertebral articulations in the lumbar region with pain on movement and pressure. At the same time severe pain developed in the right hypochondrium, slight fever and marked jaundice. The urine contained much bile pigment.

Diagnosis showed local streptococcal infection followed by acute arthritis, spondylitis and cholecystitis or cholangitis.

The blood culture gave a long chained, hemolytic streptococcus.

Autogenous vaccine treatment was combined with internal administration of elixir of iron, quinin and strychnin. Recovery was steady. Six weeks after the treatment began all symptoms had disappeared. There was no recurrence.

7.—Woman, aged 30. For 12 or 15 months the joints of the hands, wrists, ankles and feet had been very sensitive to pressure and movement. Joints were becoming progressively larger and limited as to motion. The involvement was so general and so severe that she was obliged to give up all work. The temperature showed irregular elevations of about 1.4 F. Roentgen rays showed marked increase of osseous tissue about the ends of the bones adjacent to the involved joints.

There was a history of tonsillar trouble, but the tonsils had been removed soon after the onset of arthritis with no effect on its development.

The 1st 3 blood cultures were negative; the 4th, taken after massaging and manipulating the involved joints, gave a nonhemolytic streptococcus.

Vaccine was prepared and administered continuously for 3 months, a part of which time the patient was kept at rest and given syrup of iodid of iron. The joint tenderness disappeared, the progress of the disease stopped, and she resumed work. A year later the joint trouble again became active and she was obliged to give up work. Roentgen-ray examination of the mouth showed an abscess about the root of a dead tooth. The pus pocket at the root of the tooth was removed and cultures of the pus gave streptococci mixed with diphtheroid bacilli. Autogenous vaccine treatment was persistently carried out, using a mixture of these organisms. For 6 months the patient has been free from symptoms and has worked uninterruptedly. The numerous enlargements about the joints have gradually become smaller with increased mobility of the joints.

8.—Man, aged 46. For past 4 weeks patient had pain and swelling in almost every joint with a low, irregular fever, fine petechial hemorrhages, most numerous over the abdomen; slight cough.

Moist râles were over base of lungs. The heart was enlarged markedly to the left. Low systolic murmur at apex; 1st and 2nd heart sounds feeble. The spleen was enlarged; the liver palpable. Hemoglobin 73%. White cells 17,000, 90% polymorphonuclear. The urine was scanty, containing albumin, a few pus cells and numerous granular casts. The joints were sensitive to pressure and motion, but showed no redness nor enlargement.

Diagnosis showed acute ulcerative endocarditis, acute nephritis, and acute arthritis.

The blood culture gave a nonhemolytic streptococcus which grew in firm discrete colonies and produced slight greenish color on blood agar.

Growth from a 24-hour blood slant was injected intravenously into a young rabbit. The rabbit soon lost weight, refused food, heart rate became rapid, and the animal evidenced pain on motion. At necropsy 9 days after injection, the heart and skeletal muscles were found pale and flabby; the mitral valve was nodular and contained areas of hemorrhage; the kidneys were pale; the left knee joint was dry and reddened; the hip joint contained an increased amount of serofibrinous fluid. A streptococcus like the one described was isolated both from the joint fluid and from the heart valve.

The patient did not recover.

The results in the animals inoculated with the organisms from blood cultures illustrate strikingly the localization of infection in

tissues corresponding to those infected in the patient. It is as if these freshly isolated strains have a specific selective affinity, as claimed by Rosenow, for certain tissues.

The association of joint involvement with endocardial infection, nephritis, and in 2 of these cases with infection of the bile passages is also worthy of note.

Attention is called to the teeth and tonsils, as well as to so-called 'grip' and local skin infection as original portals of entry for infection, which after entry may manifest itself in a variety of forms.

The results of autogenous vaccine treatment combined with tonics and hygienic measures seem good. An exception must be made in regard to cases with endocardial lesions in which in our experience autogenous vaccines are of no value.

Since detailed histories of all cases of joint infection in which we made cultures from the blood would be largely repetitions of the main points illustrated by the cases described, and would make this report voluminous, we have summarized them in Tables 1 and 2.

TABLE 1
A TOTAL OF 40 CASES OF ACUTE ARTHRITIS

Case	Duration	Probable Source of Infection	Accompanying Conditions	Results*	Remarks
1	6 days	Myositis.....	Streptococci	
2	4 weeks	Bad teeth.....	Streptococci	
3	3 weeks	Pneumonia.....	Negative	
4	7 days	Grip.....	Endocarditis.....	Streptococci	
5	6 days	Myositis.....	Negative	
6	3 weeks	Endocarditis.....	Negative	
7	3 months	Teeth.....	Diphtheroid bacillus	Vaccine with apparent benefit
8	3 weeks	Grip	Carditis.....	Negative	
9	3 weeks	Skin infection.....	Streptococci aureus	
10	4 weeks	Tonsils.....	Streptococci.....	Vaccine with apparent benefit
11	4 months	Pneumonia.....	Myositis.....	B. mucosus capsulatus	Vaccine with little benefit, if any
12	4 weeks	Otitis media.....	Neuritis	S. hemolyticus	
13	3 weeks	Acute tonsillitis.....	Myositis.....	B. mucosus capsulatus	
14	5 weeks	Pyorrhea.....	Negative	
15	4 weeks	Streptococci.....	Vaccine with no benefit
16	6 months	Nephritis.....	Streptococci	
17	4 months	Involvement of facial nerve	Diphtheroid	
18	7 weeks	Rheumatism.....	Negative	
19	5 months	Streptococci.....	Vaccine with apparent benefit
20	6 months	Gonorrhea.....	Gonorrhreal salpingitis	Negative	
4 cases				Streptococci in all 4	See case reports
16 cases				2 streptococci, 14 negative	

* Results of 40 cases of acute arthritis: nonhemolytic streptococci, 13; hemolytic streptococci, 1; B. mucosus capsulatus, 2; diphtheroid bacillus, 2; staphylococcus aureus, 1; negative, 21.

TABLE 2
A TOTAL OF 83 CASES OF CHRONIC ARTHRITIS

Case	Duration	Probable Source of Infection	Accompanying Conditions	Results*	Remarks
1	Bad tonsils and teeth	Myositis.....	Streptococcus.....	Vaccine with apparent benefit
2	Pyorrhea.....	Nephritis.....	Streptococcus.....	Vaccine with apparent benefit
3	Tonsils.....	Endocarditis.....	Negative	
4	6 years	Grip.....	Streptococcus	
5	1 year	Sinus infection.....	Negative	
6	Years	Pyorrhea.....	Myositis.....	Streptococcus.....	Vaccine with benefit
7	Chronic naso-pharyngitis	Sinus infection chronic	Streptococcus	
8	4 years	Specific urethritis	Myositis.....	Negative	Vaccine with some benefit
9	12 years	Nephritis.....	Streptococcus.....	Vaccine with apparent benefit
10	18 months	Streptococcus.....	
11	2 years	Chronic posterior urethritis	Negative	
12	Years	Frequent attacks of tonsillitis	Myositis.....	Streptococcus.....	Vaccine with benefit
13	1 year	Tonsils.....	Neuritis.....	Negative	
14	5 years	B. mucosus capsulatus	Vaccine with benefit
15	4 months	Pyorrhea.....	Extreme muscular soreness	Streptococcus.....	Vaccine with apparent benefit
16	15 years	Tonsils.....	Recurrent myositis	Negative	
17	1 month	Pyorrhea.....	Myositis.....	Streptococcus	
18	3 years	2 cultures of streptococcus in both	
19	4 years	Paralysis and neuritis	Negative	
20	6 years	Sciatic neuritis, lumbago	Streptococcus.....	Vaccine with apparent benefit
21	2 years	3 cultures B. mucosus capsulatus in all	Vaccine with marked benefit
22	14 years	Otitis media.....	Suspected tuberculosis	Diphtheroid	
23	Several years	Tonsils.....	Streptococcus.....	Vaccine with marked benefit
24	5 years	Tonsils.....	Marked ankylosis	4 cultures 1 streptococci	Vaccine, no benefit
25	4 months	Diphtheroid	
26	5 years	Diphtheroid.....	Vaccine with benefit
27	7 years	Puerperal infection	Sciatic neuritis....	Negative	
28	14 years	Extensive ankylosis	3 cultures, all negative	
29	4 months	Diplococcus, which later grew as a diphtheroid	Vaccine with benefit
30	Several years	4 cultures, all negative	
4 cases		Described in detail above.....		1 B. mucosus, 3 streptococci	See case reports
49 cases		Grouped.....		2 streptococci, 47 negative	

* Results of 83 cases of chronic arthritis: nonhemolytic streptococci, 18; B. mucosus 3; diphtheroid bacilli, 3; unidentified organisms, 1; negative cultures, 58.

DISCUSSION

From these results we believe that frequently, though not regularly, in arthritis, pararthritis, and myositis, organisms may be isolated from the blood stream by improved cultural methods. This is possible more frequently in the acute stages when the patient is in a febrile condition, and less frequently in the subacute and chronic stages of the infection. This we assume is because in the chronic stages the organisms are more deeply embedded in the affected tissues and occur less frequently free in the blood stream. As seen from the cases described above, streptococci were the organisms most frequently cultivated, and these correspond in type to those isolated by other observers from joints, glands, and tonsils of arthritic patients. In chronic cases we have been able to cultivate streptococci from a few drops of fluid aspirated from the joints or from neighboring involved bony parts in 6 of 10 cases.

We have found other organisms than streptococci in a small percentage of cases as follows: diphtheroids 4%, *B. mucosus* 4%, staphylococci 0.8%. These findings corroborate those of other observers who believe that occasionally the joint structures are infected by diphtheroids and *B. mucosus* as well as by streptococci, staphylococci, pneumococci, gonococci, typhoid bacilli, etc. Rosenow² states that the pathogenic property of the diphtheroid group of bacilli is similar to that of the streptococci and, as quoted, has isolated diphtheroids frequently from the adjacent lymph nodes in chronic arthritis. Our experience with this group of organisms in cases of various types leads us to the belief that while many strains of diphtheroid bacilli occur about the body as apparently harmless saprophytes, yet certain strains are unquestionably pathogenic, which is likewise true concerning the staphylococcus and streptococcus groups. Regarding the *B. mucosus*, Rosenow also isolated it from cases of chronic arthritis, and Dick³ has reported in detail cases of chronic arthritis as caused by this bacillus. In one of our cases this organism was cultivated from the blood on 3 successive cultures at intervals of several months.

We do not hold that the cultivation of the organisms from the blood or joints in these cases is definite proof of their causal relationship to the rheumatoid arthritis. There is the possibility present that in some instances the organism isolated was associated with some concurrent infection. Yet the isolation of these organisms cannot be

² Surg., Gynec. and Obst., 1915, 20, p. 404.

³ Jour. Infect. Dis., 1914, 14, p. 176. Jour. Am. Med. Assn., 1917, 68, p. 622.

overlooked in summing up the evidence regarding the etiology of arthritis.

The fact that the patients, from whom diphtheroids and *B. capsulatus* were isolated, improved under autogenous vaccine treatment still further suggests the causal relationship of the organism to the condition in these cases.

The results of autogenous vaccine treatment when consistently carried out were for the most part gratifying, though there were cases as noted where little or no improvement was evident. In making a statement regarding results of vaccine treatment we have not lost sight of the tendency of infection to spontaneous improvement or recovery, nor of the fact that in most of these cases improved hygienic conditions, rest and tonics were also factors. However, there is but little permanent improvement to be secured in chronic progressive arthritis by these measures alone, yet a number of our cases showed marked permanent improvement when these measures were combined with autogenous vaccines.

CONCLUSIONS

Streptococci may frequently be cultivated from the blood stream in rheumatoid arthritis.

There is evidence that the so-called diphtheroid bacilli and *B. mucosus* occasionally cause infection of the joint structures.

Autogenous vaccines combined with other measures have been followed by marked improvement in cases of arthritis of various types.